

Applicants: Paul L. Silverstein et al.

Serial No.: 10/70,149

Filed : January 18, 1981

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claims 1, 5, and 6 can be found at, inter alia, page 9, lines 3-8 and 16-20. Applicants maintain that the amendments to claims 1, 5, 6, 7 and 11 do not introduce any new matter. Accordingly, claims 1-7, 9 and 11 will be pending and under examination in the subject application upon entry of this Amendment.

Applicants annex hereto as **Exhibit A** a marked-up version of the amended claims to show the changes made relative to the previous version thereof.

Applicants respectfully request that, in view of the remarks made herein, the Examiner withdraw the outstanding rejections.

Formalities

Sequence Listing

The Examiner acknowledged applicants' submission of a paper copy of the sequence listing, corresponding computer readable form of the sequence and attorney's statement that the content of the two is the same, but required correction because a statement that the submission comprises no new matter is missing.

In response, applicants attach hereto as **Exhibit B** a Statement In Accordance With 37 C.F.R. §1.831(f) certifying that the contents of the computer readable form and paper copy submitted April 15, 1981 are the same, and raise no issue of new matter.

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Claim Objections

The Examiner objected to claim 11 as drawn towards nonelected claim 10.

In response, applicants point out that claim 11, as amended, is not drawn towards claim 10. Therefore, applicants respectfully request that the Examiner withdraw the objection to claim 11.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1-7, 9 and 11 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In response, applicants respectfully traverse the Examiner's rejection.

Briefly, claims 1-4 provide a composition of matter comprising Varicella-Zoster Virus 29p protein having an agent bound thereto, wherein the composition enters a mammalian cell upon contact therewith. Claim 5 provides a 29p protein having operably affixed thereto a lipid-soluble moiety which permits the 29p protein to be anchored to a lipid membrane. Claims 6 and 7 provide a lipid vesicle comprising the composition of claim 5, wherein the 29p protein facilitates delivery of the vesicle's contents into a mammalian cell. Claims 9 and 11 provide a method of delivering an agent into a mammalian cell, wherein the agent is bound to Varicella-Zoster Virus 29p

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protein.

The claimed invention is based on applicants' surprising discovery that the Varicella-Zoster Virus 29p protein can readily enter mammalian cells, such as neurons and lymphocytes.

In support of the rejection, the Examiner asserts that the specification and the prior art do not provide a structural/functional basis for one skilled in the art to envision a sufficient number of combinations of 29p variant/bound agent/target cell receptor to describe the claimed genus of such combinations. In essence, the Examiner asserts that neither the specification nor the prior art teach what are "naturally-occurring" variants of the 29p protein and the "agents" attached thereto.

In response, applicants maintain that the specification provides written description for the subject matter claimed. First, it is unnecessary that applicants set forth the sequence(s) of naturally occurring 29p protein variants for the written description requirement to be satisfied. Applicants maintain that the 29p protein having SEQ ID NO:2 and capable of entering a cell constitutes a representative number of p29 species for the purpose of written description, given that identifying naturally occurring variants thereof would require no undue experimentation.

Applicants further note that, contrary to the Examiner's position, no structure/function relationship need be established for the claimed invention to be adequately described. Indeed, it is sufficient for written description that the 29p protein has been shown by applicants to enter

mammalian cells and all methods existed in the art for affixing agents to a protein without eliminating the protein's functional properties. Applicants need not teach the specific p29 protein suitable responsible for cell entry for this purpose.

In addition, applicants point out that the term "agent" is clearly defined in the specification at, *inter alia*, page 3, lines 12-26, and examples of agents are provided at, *inter alia*, page 4, lines 1-13 and page 13, lines 1-14.

Finally, applicants stress that in this invention, the p29 protein need not have an affinity for, or naturally bind to, the agent. Rather, in certain embodiments, the protein must simply be "bound" to the agent by any means, such as covalent attachment. This point is made in response to the Examiner's statement that "each claim is drawn towards a potentially broad genus of variants of CB1 II NC11 that must retain the ability to bind any agent" (emphasis added).

Accordingly, applicants maintain that the subject matter of the rejected claims is adequately described in the specification.

The Examiner also rejected claims 4-7, 9 and 11 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response, applicants respectfully traverse the Examiner's rejection. Applicants' traverse is based, where applicable,

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on the reasons set forth in response to the Examiner's written description rejection, and on the following reasons.

The test for enablement is whether one skilled in the art could, at the time of the invention, make and use the claimed invention based on the disclosure and information known in the art without undue experimentation. Applicants maintain that the claimed invention satisfies the test for enablement, and that the Examiner has not set forth sufficient grounds for concluding otherwise.

In support of the rejection, the Examiner asserts that it would require undue experimentation to make and use the claimed invention. Specifically the Examiner asserts that in view of the factors detailed in In re Wands, (i.e., nature of the invention, breadth of the claims, guidance of the specification, working examples, state of the art, and predictability of the arts), undue experimentation would be necessary to practice the invention.

Applicants respectfully disagree with the Examiner's position. First, applicants disagree with the Examiner's characterization of the instant invention as having a "complex" nature. This invention involves delivery of an agent into a mammalian cell via a protein shown by applicants to do so. Applicants do not see this as a complex invention.

Second, and contrary to the Examiner's position, applicants note that the breadth of the claims is relatively narrow, in that only mammalian cells are recited (as opposed to "any target cell type" as stated by the Examiner). The Examiner's assertions regarding naturally occurring 23p protein variants are addressed above.

Third, applicants maintain that the specification provides adequate guidance for practicing the claimed invention. That is, the experiments in the specification showing 29p entry into mammalian cells, combined with routine methods of affixing agents to proteins and identifying naturally occurring protein variants, would enable one to practice the invention as claimed without undue experimentation. Thus, appropriate guidance is provided by the specification.

Fourth, as to the state of the art, applicants agree with the Examiner that the concept of using 29p protein to deliver an agent into a target cell is novel. However, applicants also note that the concept of using a protein that can readily enter a mammalian cell to deliver an agent to the cell was known in the art.

In support of this point, applicants annex hereto as **Exhibit C** a copy of U.S. Patent No. 5,674,980 issued on October 7, 1997 to Frankel et al. ("the '980 patent").

The '980 patent relates to HIV tat protein, a molecule which is capable of readily entering cells. Specifically, the '980 patent states that the "invention relates to delivery of biologically active cargo molecules, such as polypeptides and nucleic acids, into the cytoplasm and nuclei of cells in vitro and in vivo. Intracellular delivery of cargo molecules according to [that] invention is accomplished by the use of novel transport polypeptides which comprise HIV tat protein...covalently attached to cargo molecules." (abstract, emphasis added). Thus, precedent exists for delivering an agent into a cell via attachment to a protein capable of entering the cell.

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Applicants desire to maintain that the rejected claims are enabled.

In view of the above remarks, applicants respectfully request that the Examiner withdraw the rejection of claims 1-7, 9 and 11 under 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1-7, 9 and 11 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

In support of the rejection, the Examiner asserts that the term "top" in claims 1-7, 9 and 11 is unclear. In addition, the Examiner also asserts that the term "desired agent" in claims 1 and 7 is open to interpretation by the skilled artisan and that the term "the protein" in claim 5 renders that claim vague and indefinite.

In response, applicants traverse the Examiner's rejection, noting that amended claims 1-7, 9 and 11, either do not recite these terms or do not recite them in the manner objected to by the Examiner.

In view of the above remarks, applicants maintain that amended claims 1-7, 9 and 11 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Conclusion

Applicants maintain that claims 1-7, 9 and 11 are in condition


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for allowances, and thus, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing the prosecution of the above application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,


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<p>I hereby certify that this application was filed in the Department of the State, New York, and is a true and correct copy of the original as filed.</p> <p> 1/22/03</p> <p>Alan D. Silverstein Registration No. 28,678</p>
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Marked-Up Version of the Amended Claims

1. (Amended) A composition of matter comprising Varicella-Zoster Virus 29p protein having [bound thereto] an agent [whose delivery into a eukaryotic cell is desired]bound thereto, which composition of matter enters [the]a mammalian cell upon contact therewith.
5. (Amended) A composition of matter comprising a Varicella-Zoster Virus 29p protein having operably affixed thereto a lipid-soluble moiety which permits the 29p protein to be anchored to a lipid membrane.
7. (Amended) The lipid vesicle of claim 6, wherein the vesicle's contents comprise an agent [whose delivery into a cell is desired].
9. (Amended) A method for delivering an agent into a [eukaryotic]mammalian cell comprising contacting the agent with the cell, wherein the agent has bound thereto Varicella-Zoster Virus 29p protein which enter the cell upon contact therewith, thereby delivering the agent into the cell.
11. (Amended) The method of claim 9 [or 10], wherein the [eukaryotic]mammalian cell is a human cell.